Therapy-related acute myeloid leukemia with germline $TP53$ mutation (Li-Fraumeni syndrome)

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Clinical History

HPI: 44 year old Caucasian female referred for evaluation of pancytopenia discovered on routine CBC.

PAST MEDICAL HISTORY:

– Bilateral breast carcinoma diagnosed at age 34 treated with chemotherapy and radiation
– Squamous cell carcinoma of the scalp diagnosed at age 35
– Post-radiation spindle cell sarcoma of the left breast diagnosed at age 41
– Moderately differentiated adenocarcinoma of the rectum diagnosed at age 44
Clinical History

FAMILY HISTORY:

- 1 son deceased at age 3y for malignant brain tumor
- Mother deceased at age 34 from metastatic adenocarcinoma of unknown primary
- 1 maternal uncle deceased from bladder cancer at age 50’s

PHYSICAL EXAM: No evidence of organomegaly or lymphadenopathy, mild right lower extremity erythema
Bone Marrow Aspirate (20X)
Bone Marrow Aspirate (100X)
Bone Marrow Aspirate (100X)
Flow Cytometry

• Myeloblasts comprised 8% of events
  – Expressed CD13, CD33, CD34, CD38, partial CD117, HLA-DR, and moderate CD45
  – Partial aberrant coexpression of CD7 and CD56

• Monoblasts comprised 20% of events
  – Expressed CD4, CD13, CD14, partial CD15, CD33, CD38, CD64, HLA-DR, and CD45
  – Partial aberrant coexpression of CD56
Cytogenetic Analysis

- Ten metaphases with 47 chromosomes
  - Monosomy 4, 7, and 13
  - Additional chromosomal materials of unknown chromosome origins attached to chromosomes 4p16, 5q11.2, and 17p13
  - Two marker chromosomes and two ring chromosomes of unknown origin

- The remaining 10 metaphases appeared normal

- 47, XX, -4, add(4) (p16), add(5) (q11.2), -7, -13, add(17) (p13), +mar1, +mar2, +r1, +r2[10]/46, XX [10]
Molecular Studies

• Negative for NPM1, DNMT3A mutations
• Silent sequence variation in exon 17 of the KIT gene at codon 798
• Hemavision multiplex PCR panel: No translocations detected
Additional Molecular Studies

• Buccal swab DNA sequencing
  – A pathogenic variant c.610delG (p.E204SfsX43) was detected in the TP53 gene
Bone Marrow Biopsy- p53 IHC (40X)
Summary of Findings

• 44-year-old female referred for evaluation of pancytopenia discovered on routine CBC
• Significant past medical history and family history of malignancy
• Blasts comprising 23.6% of nucleated cells in the bone marrow aspirate, expressing a myelomonocytic immunophenotype
• Significant background trilineage dysplasia
• Complex cytogenetic abnormalities
• Pathogenic TP53 gene mutation detected on buccal swab analysis
Diagnosis

• Therapy-related acute myeloid leukemia
• Genetic studies and family history consistent with Li-Fraumeni syndrome
Li-Fraumeni Syndrome

- Prototypical familial cancer predisposition syndrome caused by germline mutations in the tumor suppressor gene \textit{TP53}, encoding the TP53 transcription factor
  - TP53 plays a central role in preventing proliferation of cells with damaged DNA
- Autosomal dominant inheritance pattern
- Classic spectrum of tumors: soft-tissue sarcomas, osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma (six common “core” cancers)
  - Breast cancer most common in adult females
  - Soft tissue sarcoma and osteosarcoma most common in children and adolescents
  - Risk for additional malignancies, many of which develop at a younger age
Li-Fraumeni Syndrome

• Classic LFS diagnostic criteria
  – Proband diagnosed with sarcoma before age 45 years
  – AND first degree relative with a cancer diagnosed before age 45 years
  – AND a first degree or second degree relative with any cancer with onset before age 45 years OR a sarcoma at any age

• 2009 Chompret diagnostic criteria
  – Proband with core LFS tumor before 46 years of age
  – AND at least one first degree or second degree relative with LFS-core tumor (except breast cancer if the proband has breast cancer) before 56 years of age OR with multiple tumors
  – Proband with multiple tumors (except multiple breast tumors), to of which are core LFS tumor types, first of which had to occur prior to age 46 years
  – Any patient with adrenocortical carcinoma or choroid plexus carcinoma irrespective of family history
References

